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For reasons contained in the Body of the Report, this study will require another 3 months to complete. We are employing an existing extensive data base on a cohort of patients treated consecutively between October 1976 and June 1978 who were free of recurrent breast cancer 10 years after diagnosis. This data base includes prospectively acquired information (regarding clinical characteristics, intraoperative factors, pathological factors) and annually updated medical and cancer history. The medical records have been reviewed for specific anatomical and surgical technique factors that were not part of the original data base. We are interviewing each survivor for a wide range of factors occurring since her cancer treatment, concerning upper extremity activity, function, injury, infection, as well as general activity and health status. We are collecting objective self-reported measurements of arm circumferences. With this study design, we will calculate incidence and rate of lymphedema development. In a nested case-control analysis the women with lymphedema will be matched with women of the same age and stage without lymphedema in order to identify differences that may be predictive of lymphedema development.

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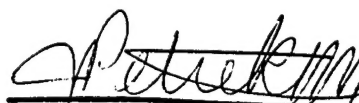

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Overview of Lymphedema: At least 15% to 20% will develop lymphedema even after modern breast cancer treatment. Lymphedema incidence in five reports published within the last ten years was about 20%.[1-5] The range was 16% to 25.5% of the study populations measured at various intervals after treatment with arm circumferences or volumetric equipment. It is striking that the reported proportion with lymphedema is similar since these patients underwent different procedures for breast cancer treatment in three different countries.

It is estimated that 1-2 million breast cancer survivors are alive today and at least 200,000 of them cope daily with the disfigurement, discomfort and disability of arm and hand swelling. Despite the human cost, lymphedema has not been systematically studied.

Of all the permanent complications of breast cancer treatment, lymphedema is the most troublesome: The cosmetic deformity can not be disguised with normal clothing, physical discomfort and upper extremity disability is associated with the enlargement and recurrent episodes of cellulitis and lymphangitis may be expected in this setting. Added to the physical symptoms is the distress caused unintentionally by the clinicians, interested in cancer recurrence, who trivialize the non-lethal nature of lymphedema.

Parallel studies by the principal investigator: Dr. Jeanne A. Petrek, Principal Investigator, has completed and ongoing protocols involving short and long term complications after breast cancer treatment. (The only major long-term complication is lymphedema.) The research projects concern randomized exercise programs and intraoperative drain techniques and were published in major surgical journals.[6,7] The patients in these prospective research projects are being followed for lymphedema development. They comprise a group of over three hundred relatively recent patients with prospectively gathered clinical, pathologic, and other variables, including preoperative arm measurements by the research nurse. However, these patients require further followup for more meaningful data on lymphedema development since mean followup is only 6.4 years.

Nature and Intent of the Present Work: We wish to document the incidence, time course, and predictive factors for lymphedema in the survivors of a breast cancer cohort. The current lack of knowledge of factors influencing lymphedema development mandates that all patients be instructed in the same arm and hand care precautions which may be too severe for those at low risk and yet not aggressive enough for those at the highest risk. The aim of the current project is to form a scale of risk for lymphedema depending on variables present at initial treatment and in the subsequent years. Prospective studies would then be performed to validate the scale of risk. As the longterm objective, future patients

could receive more individualized anti-lymphedema precautions and a specific followup schedule for early detection of this complication depending upon their risk category.

Experimental Methods: The following experimental methods were scheduled to be performed and the goal reached by the principal in a two year time interval. Because of various time-intensive followup procedures in contacting the living patients, the project is 3 months behind schedule stated in the Statement of Work in the proposal application. The Body of this annual report addresses the schedule delay.

The investigators possess a data base on 1,216 breast cancer patients treated consecutively between 1976 and 1978. It includes epidemiologic information gathered by interview at time of diagnosis, a detailed pathologic analysis, and initial/subsequent cancer and other illness treatment with followup status determined annually. Less than 2% have been lost at followup at 10 years. Much of the research assistant efforts is directed to finding these patients who, as they age become less available for easy access to interview and followup of their clinical status. Study data includes subjective enlargement and arm circumference measurements, as well as factors previously reported: age, obesity, extent of dissection, axillary radiation, and arm cellulitis/lymphangitis. The principal investigator's ongoing prospective studies have suggested: breast size, previous arm trauma/surgery, previous breast biopsy, number/proportion of positive lymph nodes, dominant hand on the treated side, specific surgical techniques and postoperative fluid formation. Factors in the subsequent years involving arm and general activity, infection and general health, etc. will be studied: occupations, sports, and hobbies, weight change, other illnesses, and arm/hand infections, injuries and surgeries.

Computer files from the existing database and the study data on arm/hand measurements and factors obtained by interview will be linked. Statistical analysis will include univariate and multivariate tests for the rate and a nested case control analysis for providing the odds ratio of lymphedema development related to various factors. Categories will be formed and risk of lymphedema will be rated according to pertinent variables present at time of diagnosis or in the ensuing years.

Body of Final Report

This research project is approximately 2 to 3 months behind schedule due to delay of tasks 2a and 2b. See below "Addressing tasks in the statement of work". Furthermore, it has required a larger budget for extra procedures in determining the status of the remaining small proportion of study subjects and in determining the location of those study subjects who are living. Departmental research funds will be able to cover these new research procedures as they were not part of the research proposal.

Addressing tasks in the statement of work and delay of schedule

In the Appendix page 11, please see the Statement of Work for the project "Lymphedema: Incidence, Time Course, and Etiologic Factors in Long Term Survivors of a Breast Cancer Cohort" that was included in the Army grant application DAMD17-94-J-4276.

Task 1a and Task 1b was achieved with multiple revisions for the appropriate data collecting instruments and returns to pilot testing on non-protocol patients who were being seen for routine followup and were similar in age and type of treatment to the study subjects.

Under task 2a and 2b, the actual interviewing process and collection of self-reported measurements has been accomplished on 227 living subjects, the result of which is now the largest study of lymphedema. Twenty-six (26) were unable to fully participate for various reasons, the most common reason being Alzheimer's Disease. Nineteen (19) patients refused participation. Of those documented as deceased, 25 have died of breast cancer and 56 have died of other causes. As evidenced by these numbers, there has been excellent co-operation among those contacted. The self-reported measurements have required more research nurse intervention with followup phone calls and reminders than predicted.

The unpredicted delay in adhering to the Statement of Work has occurred in contacting the final 146 women who were ten-year survivors but have since been lost to followup. Since the mean age of these women is 76.4 years, it is likely that most have died either of breast cancer or of other causes. Nevertheless, there is no documentation of their status through all the normal channels. Therefore, we have received permission with an official application from the appropriate sources to have a search conducted by the National Death Index. Although the grant proposal did not consider this option and did not request money in the budget, the money for this activity has been made available from departmental research funds. We predict that at least 100 will have been shown to have died in the National Death Index, at the expense of approximately $4.80 per search. The remaining

patients, perhaps 40 or 50, will be assumed to be living and will be searched through Equifax Government and Special Systems at a cost of approximately $20. per search. These patients can then be asked to join this study.

Ongoing data entry is proceeding on schedule, as listed in Task 2c.

Task 2d, report at Year 1, was completed.

Task 3a, data analysis, is provided in the folowing results section as a preliminary analysis on the first 200 women who have completed the research protocol.

Preliminary results

Outline of data collection Lymphedema was defined as an increase of 2 cm between the ipsilateral and contralateral arm differences. Clinical, anatomic, pathologic and treatment variables were obtained prospectively. Data concerning arm infection/injury, physical activity, arm exercise, weight change and life events in the followup years were obtained by interview.

The prospectively gathered (in 1978-1978) variables are part of the lymphedema database: age, race, height/weight at diagnosis, obesity, menopausal status, previous medical history, medications, size of breast (weight of mastectomy specimen), dominant hand on the treated side, cancer primary size, histologic type/other characteristics, number/proportion of lymph nodes excised with metastatic cancer, perinodal spread.

Several variables present at time of operation in 1976 to 1978 were not collected at that time but were available from review of medical record. These include various specific anatomical and surgical factors: excision of thoracodorsal nerve complex, excision of pectoralis minor muscle, length of operation, number of lymph nodes excised, highest level of lymph nodes excised, and specific on postoperative fluid formation, such as total volume of drainage and number of days with the drain.

Information obtained from interview consists of weight changes over the interval from diagnosis to the current time, illnesses, operations, medications, hospitalizations (to confirm the pre-existing database information of the annually updated medical history and cancer status), predominant occupation, hobby, sports in the years since diagnosis (for assessment of general and upper extremity activity level), and arm infection/injury or unrelated arm surgery with detailed data on time of occurrence, length of hospitalization and disability.

Preliminary results - incidence Of the first 200 study subjects, 16.4% had

lymphedema as defined. Maximum recorded arm circumference difference was 10 cm found in 1 patient.

Preliminary results - time course In the followup years after surgery, there was no interval of increased or decreased lymphedema development; There was a constant rate of women per year with onset of lymphedema.

Preliminary results - etiology None of the variables concerning events in the years subsequent to the surgery collected by interview were yet analyzed. These variables include about one-third of the data collection. A preliminary multivariate logistic regression analysis was performed to analyze other factors associated with the presence of lymphedema. These include age, body mass index (obesity), bra size, chest circumference, level (II vs. III) of axillary dissection, number of positive lymph nodes, excision of the pectoralis minor muscle, excision of the thoracodorsal complex, specific surgeon, dominant hand on the operated side, postoperative drainage volume, duration of drainage, postoperative breast radiation, and reconstruction. Although none were significant ($p < 0.05$), the following four variables closely approached significance: obesity, seroma duration, and postoperative breast radiation in that order.

Conclusions

We are employing an existing extensive data base on a cohort of patients treated consecutively between October 1976 and June 1978 who were known to be free of recurrent breast cancer 10 years after diagnosis. The existing data base includes prospectively acquired information (regarding clinical characteristics, intraoperative factors, pathological factors) and the annually-updated medical and cancer history. The medical records have been reviewed for specific anatomical and surgical technique factors that were not part of the original data base but may be associated with lymphedema development. We are interviewing each survivor for a wide range of factors occurring since her cancer treatment, concerning upper extremity activity, function, injury, infection, as well as general activity and health status. We are collecting subjective measurements of lymphedema as well as objective self-reported measurements of arm circumferences with a method tested in non-protocol patients.

With this study design, we will have an accurate incidence and rate of lymphedema development of long-term survivors of a cohort of consecutively treated breast cancer patients. In a nested case-control analysis the women who developed lymphedema will be matched with women of the same age and stage who did not develop lymphedema in order to identify differences that may be predictive of lymphedema development. The odds of developing lymphedema according to the various factors will be calculated. A profile of the patient at low, middle, or high risk for lymphedema development will be constructed.

This analysis is urgent for the potential benefit of future breast cancer patients. Currently each woman is given instructions for arm/hand precautions without taking into account the individual risk factors pertaining to lymphedema development in that woman. However, a more biological approach would be individualization for the prevention precautions and a followup schedule for early detection of this complication based on the patient's risk. The high risk patient should be admonished in detailed precautions, with reminders at surgeon, radiotherapist, and medical oncologist visits and careful circumference or volumetric measurements at that time. The highest risk patients might fit into a pilot study for aggressive prevention and be fitted with a compression sleeve immediately after surgery. Conversely, patients at low risk would not be advised in the current set of instructions which ban vigorous exercise and even carrying one's purse on the treated side. The low risk would benefit since they could have greater normalcy in their life. Most patients, however, would probably be in the average risk category and still receive the same instructions in arm/hand precautions.

For the reasons stated above, the research project has been delayed. We will continue and complete this research project in three months.

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APPENDIX

STATEMENT OF WORK

Lymphedema: Incidence, Time Course, and Etiologic Factors in Long Term Survivors of A Breast Cancer Cohort

Task 1. Months 1-2

a. Final preparatin of data collecting instruments.

b. Pilot study on non-protocol patients seen for routine followup.

Task 2. Months 3 -14

a. Interview of study subjects.

b. Collection of self-reported measurements.

c. Ongoing data entry.

d. Report at Year 1

Task 3. Months 15 - 24

a. Data analysis.

b. Manuscript/report.

Bibliography of all publications, meeting abstracts, and list of personel receiving pay from the negotiatied effort

Publications: none

Publications in which this research project is discussed

1. Petrek JA, Lerner R. Lymphedema: Etiology and treatment. In: Eds. JR Harris, ME Lippman, M Morrow, S Hellman. Diseases of the Breast. 1st Edition. JB Lippincott, Philadelphia, 1995:896-901.

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Meeting Abstracts: none

Personnel

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3. May Nah Ho, MS